Hemolytic-Uremic Syndrome—An Outbreak in Sacramento, California

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Between July and November 1982, 14 cases of the hemolytic-uremic syndrome occurred in the Sacramento, California, metropolitan area; 9 of the 14 patients lived within a 7.5-mile radius in northeast Sacramento, 10 were female, 12 were white non-Hispanic and 13 were children with a mean age of 3.6 years. Of the 14 patients, 13 were admitted to hospital; 7 required peritoneal dialysis. The 14th child, a 3-month-old white female infant, was found dead in her crib and had renal histopathologic findings consistent with the hemolytic-uremic syndrome. Of the 13 nonfatal cases, 12 patients had diarrhea before being admitted to hospital. A case-control study involving 11 cases and 22 controls did not show any significant differences in exposure to a variety of possible risk factors including restaurants, specific foods and water supply. Stool specimens were negative for enteric bacterial pathogens by culture and for viruses by tissue culture assay, suckling mouse inoculation and immune electron microscopy; no serologic evidence was found for infection due to enteroviruses, respiratory viruses or arenaviruses. Two of four children tested, however, showed serologic evidence of infection by Vero-cytotoxin-producing Escherichia coli. *These 14 cases represent one of the largest reported outbreaks of the hemolytic-uremic syndrome in the United States.*

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The hemolytic-uremic syndrome is comprised of the triad of microangiopathic hemolytic anemia, thrombocytopenia and nephropathy. It primarily affects previously healthy preschool-age children and most often occurs following a diarrheal prodrome or, less commonly, a respiratory prodrome.[1] Argentina,[2] South Africa,[3] The Netherlands[4] and California[5] account for many of the reports. Most cases occur sporadically and have been reported in association with enteroviruses,[6] Microtatobiotes,[7] *Campylobacter*,[7] *Yersinia*[9] and Vero-cytotoxin-producing *Escherichia coli*,[10] including a rare *E coli* serotype 0157:H7 that has been associated with hemorrhagic colitis.[11] Several clusters of between 9 and 14 cases have been reported, some associated with *Shigella dysenteriae* type 1,[12] and one with echovirus 22.[13] One unusual outbreak of 14 cases in Ontario was associated with ingestion of unpasteurized apple juice, but no specific organism or toxin was incriminated.[14]

An outbreak of 14 cases of the hemolytic-uremic syndrome that occurred in Sacramento, California, in the summer and fall of 1982 provided an opportunity to investigate possible risk factors associated with the disorder. We describe that investigation and its outcome.

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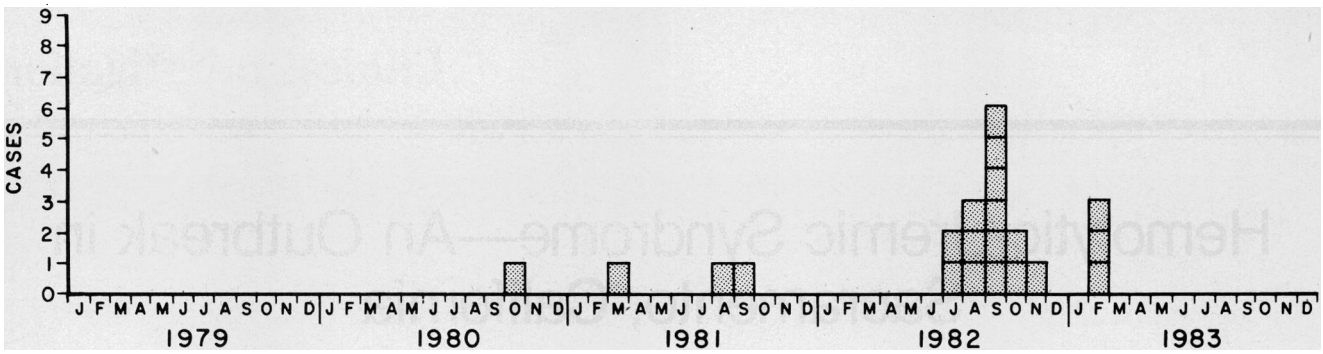

Figure 1.—Hemolytic-uremic syndrome by month of onset, Sacramento, California, 1979 to 1983.

Patients and Methods

Epidemiologic Investigation

A case of hemolytic-uremic syndrome was defined as one diagnosed by a physician and characterized by an abrupt onset of (1) microangiopathic hemolytic anemia (hematocrit of less than 35% and a peripheral blood smear showing fragmented erythrocytes); (2) thrombocytopenia (platelet count less than 150,000 per μl, and (3) nephropathy (one or more of the following: hematuria, proteinuria, serum creatinine level of more than 0.8 mg per dl or blood urea nitrogen value of more than 20 mg per dl).

Cases were ascertained by contacting the two pediatric nephrologists practicing in the Sacramento area, by surveying all hospitals with pediatric beds in Sacramento County and three adjacent counties and by contacting the Sacramento County Health Department.

To identify potential risk factors associated with this disease, a case-control study was done. Of the 14 epidemic cases known to us at the time of the investigation, 11 were included in the case-control study. For each patient with the hemolytic-uremic syndrome, two control children were matched for sex, race and age—within 3 months for children younger than 1 year, within 6 months for children from 1 to 2 years of age and within 12 months for children older than 2 years. Control children were chosen at random from the practice of the primary care physician or the health maintenance organization of a child with the syndrome. Children with chronic diseases were excluded. All parents of control children who were asked agreed to participate.

A standardized questionnaire was administered to the parents of affected patients and control children. Questions concerned experiences during the one-month period before the onset of the prodromal illness in a child with the hemolytic-uremic syndrome. Data from the case-control sets were analyzed by the Mantel-Haenszel estimate of the odds ratio for multiple controls per case. When appropriate, relative risks were calculated. Confidence limits were calculated as proposed by Miettinen.[15]

Laboratory Investigation

Throat swab specimens from three patients, urine specimens from two patients and stool specimens from five patients and from one patient's father (who had bloody diarrhea) were collected within five to eight days of onset of their diarrhea. Stool extracts and urine were cultured for viruses as previously described[16] by inoculating suckling mice intraperitoneally and cell cultures, including primary rhesus monkey kidney cells, human rhabdomyosarcoma cells, human fetal kidney cells and human embryonic lung fibroblast cells. Throat-swab specimens were cultured for viruses by inoculating cell cultures including primary rhesus monkey kidney cells, human embryonic lung fibroblasts and HEp-2 cells.[16] Organisms were identified by standard neutralization tests.[17]

Stool suspensions were examined for viral particles using immune electron-microscopy techniques as previously reported,[18] with the exception that bacteria were removed from the stool suspensions by differential centrifugation.

Stool specimens were also examined for bacteria including *Salmonella, Shigella, Campylobacter, Yersinia, E coli* including type 0157:H7[19] and Vero-cytotoxin-producing *E coli*, and for the presence of free Vero-cytotoxin in stool filtrates.[10]

Acute- and convalescent-phase serum specimens obtained from seven patients were tested for antibody to prototype strains of Coxsackie viruses types A16 and B1-6 and echoviruses types 9, 11, 22 and 30 by standard microneutralization tests,[20] for antibody to adenovirus, parainfluenza viruses types 1 to 3, influenza A and B viruses, respiratory syncytial virus and *Mycoplasma pneumoniae* by complement fixation,[21] and for Vero-cytotoxin-neutralizing antibody as previously described.[10] Serum specimens were also tested for antibody to members of the arenavirus group because many of these viruses cause hemorrhagic fever accompanied by renal failure. The indirect fluorescent antibody test with antigens prepared as previously described[22] was used to test for antibody to Hantaan virus, lymphocytic choriomeningitis virus, Junin virus, Machupo virus, Ebola virus (both Mayinga and Boniface strains) and Marburg virus.

Results

The Patients

Between January 1979 and October 1982 (the time of the investigation), 18 cases of the hemolytic-uremic syndrome were identified (Figure 1). Three other cases occurred in February 1983 and were reported to us through an ongoing surveillance established at the time of the investigation. Four cases occurred between January 1979 and June 1982, for a yearly incidence of 0.41 cases per 100,000 children younger than 14 years. In contrast, 13 cases in children and 1 case in an adult occurred in a four-month period between July and November 1982, for a yearly incidence of 11.2 cases per 100,000 children younger than 14 years. These 14 cases were identified as the epidemic cases.

The 13 children had a mean age of 3.6 years (range, 2 months to 11 years). Of the 13 children, 9 were girls; 11 were

white, non-Hispanic; 1 was black, and 1 was Hispanic. The adult case was that of a 39-year-old white woman.

Of the 14 patients, including the 1 adult patient, 12 had a diarrheal prodromal illness characterized by bloody stools (10 patients), abdominal cramping (10), vomiting (9) and low-grade fever (5). One child, an 11-year-old Hispanic boy, had jaundice, abdominal pain and anorexia for six days before admission. A 3-month-old infant was found dead in her crib on July 18 and initially had been diagnosed as having died of the sudden infant death syndrome. Autopsy findings in the kidney were consistent with a diagnosis of the hemolytic-uremic syndrome, specifically, thrombotic microangiopathy.

All 13 of the surviving patients required hospital care, 7 of the 13 required peritoneal dialysis and chronic renal failure developed in none.

Epidemiologic Investigation

The most interesting epidemiologic finding was that 8 of the 13 children and the 1 adult patient lived within a 7.5-mile radius in northeast Sacramento (Figure 2). Although the census tracts of these eight children represent only 8% of the population younger than 14 years of age in Sacramento County, 62% (8 of 13) of the cases of the hemolytic-uremic syndrome in children occurred in this area—relative risk = 18.20, 95% confidence intervals 8.15 to 40.68. The area is primarily residential and includes several suburbs that were built after 1970 on land that was previously used for agriculture. Despite the fact that several of the children were from the same area of the city, none of the children had had known contact with each other.

The cases of the hemolytic-uremic syndrome occurred in primarily middle-class families. Although not statistically significant, the mean yearly income in 13 (93%) of the 14 case census tracts was more than $20,000 (1980 national census data), whereas in Sacramento County only 86 (57%) of the 150 census tracts had mean incomes that high—relative risk = 3.72, 95% confidence intervals 0.9 to 15.31.

Because most patients had a gastrointestinal prodromal illness and because viral and bacterial gastrointestinal pathogens had been reported in association with the syndrome in the past, we focused our investigation on identifying the cause of the diarrhea and risk factors associated with the epidemic

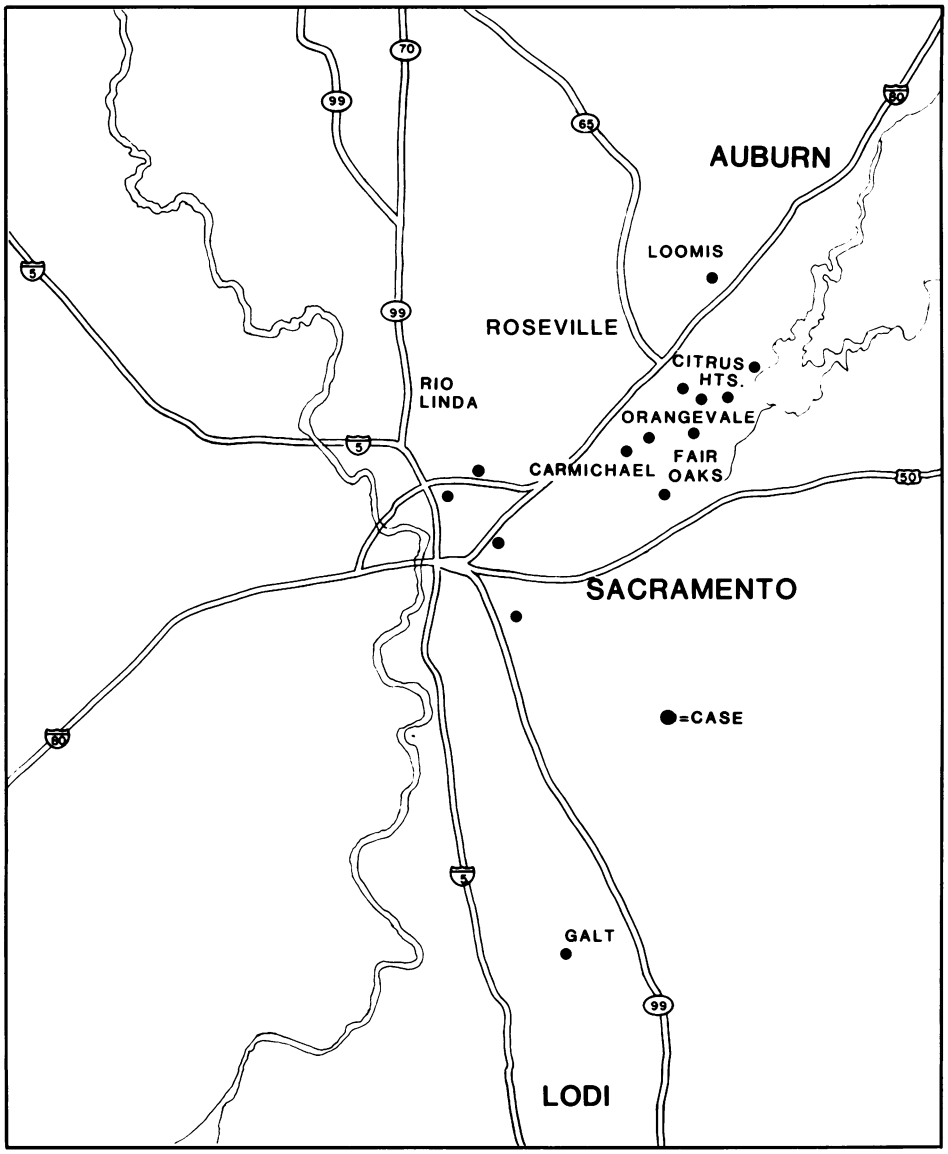

Figure 2.—Cases of hemolytic-uremic syndrome, by residence, Sacramento, California, 1982.

TABLE 1.—*Exposures Investigated in 11 Cases and 22 Controls in an Outbreak of the Hemolytic-Uremic Syndrome, Sacramento, California, 1982*

Ingestion of new foods	Medical history of allergies
Ingestion of raw milk	Swimming pools
Ingestion of unpasteurized juice	Saunas
Special diets	Vaccinations
Grocery stores or chains	Animals
Restaurants	New toys
Medications taken for diarrhea	New furniture
Day-care centers or attendance	New carpeting
Travel	Fumigation
Large gatherings	Paints
Parent's occupation	Other household chemicals

by conducting a case-control study, examining the water supply and looking for concurrent epidemics of diarrhea. Analysis of the case-control study did not reveal any exposures that differed significantly between cases and controls (Table 1), including ingestion of certain foods, exposure to a common grocery store or chain or dining at a particular restaurant or chain.

Many investigators have reported the frequent occurrence of diarrhea in the siblings of children with the hemolytic-uremic syndrome. Although not significant, 3 (33%) of the 9 children with the syndrome with siblings had a sibling with recent diarrhea, compared with 4 (19%) of the 21 control children with siblings—odds ratio = 1.5, 95% confidence limits 0.35 to 6.35.

Although cases clustered within a small geographic area, no more than two patients had the same water supply. A review of routine fecal coliform counts of these water supplies showed no evidence of contamination of any of these water supplies during 1982.

Although there was a general increase in cases of gastroenteritis during the summer and fall months when compared with the winter season, there was no increase in occurrence of gastroenteritis during September, the month of peak occurrence of the affected cases. The physicians of the patients with the hemolytic-uremic syndrome also did not report any unusual increase of cases of gastroenteritis in their practices.

Laboratory Findings

No viruses or bacterial pathogens, including *E coli* 0157:H7 or other Vero-cytotoxin-producing organisms, were found in the stool and urine specimens, and no viral particles were observed by immune electron-microscopic examination of stool specimens. One of three throat swab specimens grew adenovirus type 2. Paired serum samples from seven patients showed no fourfold titer rise or unusually high titers to the enteroviruses or the respiratory viruses, including adenovirus. Serologic tests showed no association between infection with the agents that are known to cause hemorrhagic fever and this outbreak of hemolytic-uremic syndrome.

The five stool specimens tested for the presence of free Vero-cytotoxin were negative. Two of four paired serum specimens tested for neutralizing antibody to Vero-cytotoxin showed a fourfold rise in titer from 1:8 to 1:64 in one case and from 1:4 to 1:16 in the other. The titers of the other two children tested were stable at 1:4 and less than 1:4.

Discussion

This outbreak of 14 cases of the hemolytic-uremic syndrome in Sacramento is one of the largest reported from the United States, with cases clustered both temporally and geographically. The first reported outbreak of ten cases of the syndrome occurred in 1963 in a small geographic area of North Wales[23]; no associated agent was identified. Since then, the following outbreaks have been reported: 10 cases at the Stanford University School of Medicine occurring during the year beginning October 1974[5]; 28 cases in Bangladesh occurring in 1975-1976 and associated with an outbreak of *Shigella dysenteriae* type 1[12]; 10 cases in Montreal, Canada, occurring during an eight-month period in 1977-1978 and associated with echovirus type 22,[13] and 14 cases in Toronto, Canada, occurring during an 11-day period in September 1980 and associated with ingestion of homemade apple juice.[14] In Argentina, endemic cases tended to be admitted in small groups or clusters; these cases apparently came from widely scattered areas, however.[2] Van Wieringen and co-workers reported an increase in cases in the Netherlands during 1969 and 1970, but these cases were also apparently widely scattered geographically.[4]

Although the cause of the hemolytic-uremic syndrome is unknown, many investigators suspect the disease is caused by or related to an infectious organism. In addition to echovirus 22 and *S dysenteriae* type 1 reported in association with outbreaks, sporadic cases have been reported in association with Coxsackie viruses types A and B, echoviruses types 11, 9 and 30, influenza viruses[1] and bacterial agents including *S dysenteriae* type 1, *Salmonella, Campylobacter* and *Yersinia.* A recent report from Canada[10] showed an association between the hemolytic-uremic syndrome and infection with Vero-cytotoxin-producing *E coli* including *E coli* serotype 0157:H7. This rare serotype, which has been associated with outbreaks of hemorrhagic colitis in the United States,[24] was subsequently also associated with three cases of this syndrome in England.[11] None of the patients in this outbreak who were tested were found to have any microbiologic evidence of infection with Vero-cytotoxin-producing *E coli,* although it should be noted that the stool specimens were examined for free Verotoxin more than a year after preservation at −70°C. Two of four children tested, however, showed a significant fourfold rise in Vero-cytotoxin-neutralizing antibody titer.

The late summer-early fall seasonality of this outbreak with the peak occurrence in September is typical of the endemic cases in northern California. Others report occurrence of the syndrome in the springtime (Sorrenti and Lewy, Chicago),[25] late spring-early summer (van Wieringen and associates, the Netherlands),[4] fall-winter (Gianantonio and colleagues, Argentina)[2] and summer-fall (Ray and co-workers, Kansas City and Seattle).[6] Because of the summer-fall seasonality observed by many investigators in the United States, enteroviruses have been proposed as possible etiologic agents. However, we were unable to find evidence of enteroviral infection by either tissue-culture methods or serologic means.

Little has been published concerning the socioeconomic status of children with the hemolytic-uremic syndrome. The middle-class socioeconomic status of the Sacramento children is consistent with the observation of Gianantonio and associates in Argentina and Kibel and Barnard in South Africa.[2,3]

This finding could be related to a particular type of exposure that is more commonly found in the higher classes for economic or educational reasons.

Many epidemic and endemic cases of the hemolytic-uremic syndrome are unexplained, as were the cases in this outbreak. The cause of this disease is quite likely multifactorial. The geographic and temporal clustering of these cases suggests that some factor common to these children may have been responsible for their illness. Recommended future studies of the syndrome include a national surveillance to identify regional patterns of occurrence, a continued search for organisms and toxins possibly associated with this disease and identification and investigation of epidemics to determine risk factors for disease acquisition and possible prevention.

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